REMARKS

Claims 11, 14-16, 18-26, and 28-41 remain pending in this Application. Claims 11, 14-16, 18-26, and 36 have been currently amended. Claim 42 has been added. Claims 1-10, 12, 13, 17, and 27 have been canceled without prejudice. Claims 28-35 and 37-41 have been withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected inventions. No new matter has been added.

The Office Action reports that the application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825, because no sequence identification has been provided for the nucleic acid sequences presented at p. 10, lines 31-33, p. 13, lines12-21, line 34, p. 14, lines 24-25 and p. 17, lines 7-10 of the instant specification.

The sequences cited above are not identified in the instant Sequence Listing. Accordingly, Applicants have filed herewith 1) a substitute computer readable (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, and 2) a substitute paper copy of that "Sequence Listing." The enclosed sequence listing is based on the sequence listing which was submitted during the international phase and has been amended to contain the primer sequences listed in the Specification.

Applicants have amended the Specification by directing entry of the attached paper copy of the Sequence Listing into the specification. Applicants submit that the content of the paper and computer readable copies are the same and where applicable, include no new matter, as required by 37 C.F.R. § 1.821(e) or 1.821(g) or 1.825(b) or 1.825(d). Applicants have also amended the Specification, specifically at page 10, lines 31-33, page 13, lines 12-21, line 34, page 14, lines 24-25 and page 17, lines 7-10, by including references to particular sequence identifiers (SEQ ID NO:) wherever a reference is made to that sequence.

Applicants have further filed herewith a certified English translation of the foreign application in order to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d).

The Office Action reports that the title of the invention is not descriptive. Accordingly, Applicants have replaced the instant title with a new title that is clearly indicative of the invention to which the claims are directed. Specifically, the new title is --Method of Removing Anti-AChR Antibodies from the Serum of a Myasthenia Gravis (MG) Patient Using a Combination of Recombinant Domains of Nicotinic Acetylcholine Receptor (AChR) Subunits--. Applicants consider the title as now amended clearly indicative of the invention to which the claims are directed.

Claims 16 and 24 stand objected to because the term "Pichia pastoris" recited in claim 24 is not italicized, and the terms "SFV" recited in claim 24 and "P3A" recited in claim 16, are not a common abbreviation. Applicants have amended claim 24 to

italicize the term "Pichia pastoris" and to spell out "SFV" as required by the Examiner. As to the term "P3A", the term is not an abbreviation but a denomination of an exon within the nicotinic acetylcholine receptor (AChR) as referenced on page 8, lines 43-45 of the instant Specification. Accordingly, Applicants respectfully request that this objection to the claims be withdrawn.

Claims 11-27 stand "rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Office Action reports that the claims are indefinite because the claims recite "a combination of recombinant domains derived from any one of alpha ... subunits of the primate muscle nicotinic acetylcholine receptor (AChR)." Applicants have amended the claims to remove the phrase "derived from". Accordingly, Applicants respectfully request that this rejection of the claims be withdrawn.

The Office Action further reports that the "claims 16 and 24 are indefinite because the terms 'P3A' and 'SFV' are recited in the claims without a reference to a precise amino acid sequence identified by a proper SEQ ID NO: or providing a full name for the abbreviated names." The term "P3A" refers to a denomination of an exon within the nicotinic acetylcholine receptor, and the term "SFV" refers to Semliki Forest Virus. Applicants submit that one of ordinary skill in the art would understand the meaning of the terms and determine therefrom the metes and bounds of the claims.

Accordingly, Applicants respectfully request that this rejection of the claims be withdrawn.

Claims 16, 18-22 stand "rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements." The Office Action reports that the claims only recite different amino acid residues, and omit specific sequences. Applicants submit that the claims are clear in the absence of reference to specific sequences. The claims as amended refer to N-terminal extracellular domains of the alpha, beta, gamma, delta and epsilon subunits of the human muscle AChR. Applicants submit that the AChR is a well-known molecule, and that a literature search reveals over 200 publications mentioning AChR, each of them published before the priority date of the present application.

In addition, the sequence of AChR is readily available through publications and sequences databases. Applicants have attached herewith several references disclosing or discussing the sequences of various subunits of AChR:

Schoepfer et al., 1987 and Beeson et al., 1990, each disclose the alpha subunit of AChR;

Beeson et al., 1989 disclose the beta subunit of AChR;

Luther et al., 1989 disclose the delta subunit of AChR;

Beeson et al., 1993 teach the cloning of the gamma and epsilon subunits of AChR; and

Engel et al., 1996 discloses mutations in several subunits of AChR.

Applicants further advise that the sequences of the subunits are published in databases (UniProt/SwissProt) with the following accession numbers: ACHA_HUMAN, P02708 (for alpha subunit), ACHB_HUMAN, P11230 (for beta subunit), ACHG_HUMAN, P07510 (for gamma subunit), ACHD_HUMAN, Q07001 (for delta subunit), ACHE_HUMAN, Q04844 (for epsilon subunit). Therefore, it would be clear to one of ordinary skill in the art which molecule is used. Furthermore, in reference to these and other published sequences it is also clear which part of the molecule is used in the present invention. Accordingly, Applicants respectfully request that this rejection of the claims be withdrawn.

Claims 11-27 stand "rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101." Applicants have amended the claims to include method steps involved in a method for removing anti-acetylcholine receptor (anti-AChR) antibodies from serum of a myasthenia gravis (MG) patient. Accordingly, Applicants respectfully request that this rejection of the claims be withdrawn.

Claims 11-27 and 36 stand "rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement." The present invention provides a novel method which allows the at least substantially complete removal of

anti-AChR antibodies from the sera of myasthenia gravis (MG) patients. This is achieved by using a combination of N-terminal extracellular domains of the subunits of AChR. The claims now state that it is the N-terminal extracellular domain of the molecule which is useful in the method of the present invention. It is clear to one of ordinary skill in that art that small variations in the length or composition of these subunits would not affect the method of the present invention. In this regard, Applicants submit that the actual AChR molecule and its subunits were known prior to filing of the present invention. One of ordinary skill in the art would have known at the time of filing of the present invention which parts of the AChR protein are the N-terminal extracellular domains of the alpha, beta, gamma and epsilon subunits.

Furthermore, Applicants cite Example 1 of the present application as clearly teaching how to assay the ability of the N-terminal extracellular domain (ammo acid 1-210) of the alpha subunit to bind to antibodies. Based on the disclosure in the Specification, one of ordinary skill in the art is readily able to assay any domain of any subunit of AChR for its ability to immunoadsorb antibodies.

Applicants also cite Example 2 as describing in great detail the expression of the extracellular domains of beta, gamma, delta and epsilon subunits, their purification and characterization. Based on this disclosure, one of ordinary skill in the art is readily able to provide any N-terminal extracellular domain useful in the method of the present invention. Further guidance on carrying out the invention is provided in Example 3 which discloses the immunoadsorption of antibodies from MG patients' sera with a

combination of subunits. Limiting the claims to a specific sequence would represent an unjust limitation of the invention in view of its contribution to the art. Accordingly, Applicants respectfully request that this rejection of the claims be withdrawn.

Claims 11-21, 23-27 and 36 stand "rejected under 35 U.S.C. 102(a) as being anticipated by Psaridi-Linardaki et al. (J. Biol.Chem. 2002. July, 277:2698-26986)." The rejection is hereby traversed and reconsideration is respectfully requested.

The present invention provides a method for removing anti-AChR antibodies from serum of a myasthenia gravis patient using a combination of AChR subunits for immunoadsorption of anti-AChR antibodies. The present invention uses for the first time more than one subunit to remove anti-AChR antibodies from patients' sera. The use of alpha, beta, gamma, delta and epsilon subunits complement each other. Each of the subunits is capable of eliminating a different fraction from the pool of the anti-AChR antibodies from the MG patients. The majority of antibodies are immunoadsorbed by the alpha subunit. Each of the extracellular fragments of the other subunits (beta, gamma, delta and epsilon) binds lower **but significant percentages of anti-AChR** antibodies from the MG patients' sera. This is the first time that the significance of the anti-AChR antibody binding by the other subunits has been appreciated and put into practice. The combined use of all subunits of N-terminal extracellular domains of AChR is highly preferable as it removes the majority of anti-AChR antibodies from the MG patients' sera.

Psaridi-Linardaki et al. teach the expression of N-terminal extracellular domain of the alpha subunit of AChR in *Pichia pastoris,* and propose the use of the alpha subunit in structural studies of the AChR and as an autoantigen in myasthenia gravis studies. There is no teaching or suggestion in Psaridi-Linardaki et al. of removing anti-AChR antibodies from sera. The cited reference also fails to teach or suggest immunoadsorption methods for removing anti-AChR antibodies from the sera of MG patients, especially through the combination use of the N-terminal extracellular domains of the alpha, beta, gamma, delta and epsilon subunits of AChR.

Accordingly, Applicants' invention as claimed is not anticipated nor made obvious by Psaridi-Linardaki et al. In view of the above remarks, Applicants respectfully request that this rejection of the claims be withdrawn.

Claims 11-18, 23 and 25-26 stand "rejected under 35 U.S.C. 102(b) as being anticipated by Barchan et al. (Eur. J. Immunol. 1998. 28:616-624)." The rejection is hereby traversed and reconsideration is respectfully requested.

Barchan et al. teach an antigen-specific therapy of myasthenia gravis. The therapy involves administering orally or nasally polypeptides derived from AChR to delete or induce anergy of antigen-specific T cells. This method is materially different from the immunoadsorption method claimed in the present invention. Barchan et al. fail to teach or suggest the immunoadsorption of anti-AChR antibodies from the MG

patients' sera, especially through the combination use of the N-terminal extracellular domains of the alpha, beta, gamma, delta and epsilon subunits of AChR.

Accordingly, Applicants' invention as claimed is not anticipated nor made obvious by Barchan et al. In view of the above remarks, Applicants respectfully request that this rejection of the claims be withdrawn.

Claims 11-14,17-18, 23, 25-27 and 36 stand "rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No 5578496 (cited previously)." The rejection is hereby traversed and reconsideration is respectfully requested.

US Patent No. 5578496 ("'496") is directed to the detection of human AChR autoantibodies associated with myasthenia gravis. More specifically, "496 merely discloses the use of a single subunit, namely the alpha subunit of AChR, for binding with antibodies. There is no disclosure corresponding to the beta, gamma, delta and epsilon subunits. '496 further fails to teach or suggest the use of immunoadsorption to remove anti-AChR antibodies from the MG patients' sera, especially through the combination use of the N-terminal extracellular domains of the alpha, beta, gamma, delta and epsilon subunits of AChR.

Accordingly, Applicants' invention as claimed is not anticipated nor made obvious by US Patent No 5578496. In view of the above remarks, Applicants respectfully request that this rejection of the claims be withdrawn.

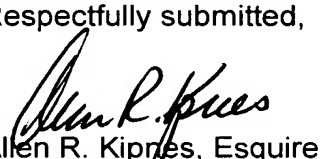
Claims 11-14,17-23, 25-27 and 36 stand "rejected under 35 U.S.C. 102(b) as being anticipated by Besson et al. (Neurology, 1996.47:1552-1555)." The rejection is hereby traversed and reconsideration is respectfully requested.

Beeson et al. relates to techniques for diagnosing MG from the patients' sera using adult and fetal AChR subunits. Beeson et al. fail to teach or suggest the use of immunoadsorption (i.e. removal of antibodies) to remove anti-AChR antibodies from the patients' sera.

Accordingly, Applicants' invention as claimed is not anticipated nor made obvious by Beeson et al. In view of the above remarks, Applicants respectfully request that this rejection of the claims be withdrawn.

In view of the foregoing, Applicants submit that the present application is in condition for allowance and early passage to issue is therefore deemed proper and is respectfully requested. It is believed that no additional fees are due in connection with this matter. However, if any additional fees are due, it should be charged to Deposit Account No. 23-0510.

Respectfully submitted,



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